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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/505,138
Filing Date: August 19, 2004
Appellant(s): DIETRICH ET AL.

Joshua Goldberg
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/30/2009 appealing from the Office action mailed 11/12/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: Appellants have used the wrong Patent Numbers for the Ghebre-Sellassie and Login patents. The correct Patent Number of the Ghebre-Sellassie patent is 6,677,362, not 6,667,362 as in the Brief; the correct Patent Number of the Login patent is 5,262,171, not 5,262,711 as in the Brief.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,677,362	Ghebre-Sellassie et al.	1-2004
5262171	Login et al.	11-1993

US Published Application 2003/0018071 to Rennard et al. January 23, 2003

Remington: The Science and Practice of Pharmacy, 1995

Chiou, "Pharmaceutical Applications of Solid Dispersion Systems" 60 J. Pharm. Sci. 1281 (1971)

Hatzelmann, et al. "Anti-inflammatory and Immunomodulary Potential of the Novel PDE4 Inhibitor Roflumilast in Vitro" 297 J. Pharm. Exp. Ther. 267 (2000)

Odian “Principles of Polymerization” 1991

PVP (Polyvinylpyrrolidone) manufacturer’s information sheet, Copyright 2007, downloaded from the world wide web on 1/22/2008

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claims 68 and 82-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims specify the "weight average molecular weight" of polyvinylpyrrolidone. As shown by the Odian reference, there are at least three different molecular weight averages of polymers: number average, weight average, and viscosity average. Notably, in any particular polymer sample each of these three types of molecular weights has a different vlaue. The original disclosure does not mention the term "weight average molecular weight" nor is there any discussion in the original disclosure of what type of average molecular weight average is being referred to. The introduction of this new limitation, not originally disclosed or even discussed, constitutes new matter.

Claim Rejections - 35 USC § 103

Claims 38, 39, 41, 45-48, 65, 69, 71-79, 81, and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remmington: The Science and Practice of Pharmacy.

Rennard teaches roflumilast, the PDE4 inhibitor of instant claims. Paragraph 0015. The roflumilast is compressed into a tablet. Paragraph 0020, Example 3. The tablet is produced by blending the ingredients, adding magnesium stearate, and compressing on a tablet press. Rennard suggests making immediate release formulations by adding excipients such as lactose, microcrystalline cellulose, starch, and magnesium stearate. Table 2.

Rennard does not teach:

(1) the addition of polyvinylpyrrolidone (PVP), and

(2) granulation on a fluid bed granulator.

Ghebre-Sellassie teaches methods of making tablets that improve the bioavailability of poorly water soluble drugs. Abstract. Ghebre-Sellassie accomplishes this by combining the drug with a polymeric carrier, preferably PVP. Abstract, col. 3 lines 34-56. The compositions are made by blending the drug with the carrier (PVP). Col. 4, lines 9-34. The mixture is transferred to a fluid bed granulator, where a solution of a plasticizer, such as PEG is dissolved with a surfactant. *Id.* The solution is sprayed onto the powder blend on the fluid bed granulator, making the granulation. *Id.* The resulting granulate can then be milled and formed into tablets or capsules. *Id.* The tablets or capsules are optionally coated with a film coating. *Id.*

Remmington teaches methods of granulation, such as dry and fluid-bed granulation. Pages 1625-26. Fluid bed granulation has the advantages of preparing uniform granules of a specified particle size and distribution, and has the manufacturing benefit of coating, lubricating and compressing the particles in the same machine rather than having to use multiple machines. Remmington describes this method as "the trend for the future." Page 1625. In a fluid bed granulation process, a solution with binder, plasticizer, etc. is sprayed onto the drug powder. Page 1625. PVP is a binder, and is used in 2% concentration solutions in water or alcohol. Page 1618. For tabletting a granulate, corn starch is an appropriate binder. Page 1618

A list of where the references teach each claim limitation, or why limitations not explicitly taught are obvious, appears below.

- The compound of claims 35, 47, 69 in an immediate release tablet as per claim 80: Rennard, paragraph 0015, 0020

- Granulation with a solution of a binder of claims 35 and 47: Remington, 1625

- Use of PVP of claims 35 and 47: '362 patent, abstract, examples

- Fluidized bed granulator of claims 41, 87: Remington, 1625

- Filler of claims 44, 48, 65, 75: Rennard, table 2; Remington, 1618

- Granulation with fillers followed by mixing with a "release agent" of claims 45 and 46, followed by tabletting: Remington, 1618, Rennard, Examples. Note that absent a definition to the contrary, lubricants such as magnesium stearate are understood to also be "release agents" as required.

- The amount of rolflumilast of claim 71: obvious to optimize dosage depending on condition being treated, the species, age, weight, and gender of the patient; Rennard table 2 (using the name ARIFLO for rolflumilast, see claim 9 and paragraph 0024, explaining that the two are the same compound) also gives information on the amount of drug

- Use of the claimed amount of PVP of claims 72, 73, binders of amount of claim 75 (PVP is binder): Remington, 1618 (although it is not clear if this teaching relates to the concentration of PVP in granulating solution or the concentration in the final product); to the extent that Remington does not disclose the claimed amount, this is merely an optimization of '362's teaching to granulate with PVP. Determining the optimal amount once the general parameters of are known is not a basis for patentability.

- Filler from 40 – 99.9%: Rennard, table 2

- Fillers and release agents of claims 78, 79, 81: Rennard, table 2

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use PVP in conjunction with the invention of Rennard, to granulate the PVP in a fluid bed granulator before mixing with an additional excipient, such as magnesium stearate, and tabletting the product. PVP is obvious to use because '362 teaches the specific advantages of said use, such as increasing bioavailability of poorly soluble drugs. Rolflumilast is known to be a poorly water soluble drug. It would have been obvious to use a wet granulation process because this process is recognized by the art as suitable for making PVP containing dosage forms, because of the advantages Remmington describes for fluidized bed granulation, and because Ghebre-Sellassie specifically teaches fluid-bed granulation using a solution (wet granulation). Because these manipulations are expressly described or suggested by the art, the artisan would enjoy a reasonable expectation of success.

Claims 68 and 82 – 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remington: The Science and Practice of Pharmacy, 1995 (cited on PTO 892 mailed 11/3/2006), as applied to claims 38, 39, 41, 44 – 48, 65, 69, and 71 – 80, 87, above, and in further view of US 5,262,171 to Login et al.

What is lacking from the teachings of Rennard, '362, and Remington is a teaching of PVP having the instantly claimed molecular weight.

Login teaches that PVP suitable for use in tablets has is graded as K-30 to K-120 molecular weight. The artisan understands that this corresponds to molecular weights

of approximately 9,700 Daltons to 3,470,000 Daltons (see PVP product disclosure, cited on PTO 892).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to find the optimal molecular weight of PVP within the range taught by Login. When the general conditions of an invention are set out by the art, finding the optimal or working conditions is not a basis for patentability. Here, the art shows that use of PVP within the useful range will give a predictable result; finding the optimal or working molecular weight of PVP will increase the bioavailability of the drug. The artisan would recognize that PVP may have a molecular weight as low as a few hundred daltons, or as high as tens of millions of daltons. Bearing this in mind, the molecular weight range taught by Login (about 250,000 daltons from low to high) fairly narrow, and the artisan would enjoy a reasonable expectation of success at finding the optimal molecular weight within that range depending on the future intended use of the product. With regard to the amounts of the other elements of the formulation in claims 82 - 84, these claims merely change the amount of active agent (a variation or optimization of dosing that is obvious to the artisan), and use an appropriate amount of fillers and binders. The use of these materials, all of which the art recognizes as useful with roflumilast and other poorly soluble drugs, is a matter of merely optimizing the amounts of excipients in a composition to give predictable results, namely an immediate release tablet as taught by Rennard with higher bioavailability as taught by Ghebre-Sellassie.

Claims 42 - 44, 53, 54, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remington: The Science and Practice of Pharmacy, 1995 (cited on PTO 892 mailed 11/3/2006), as applied to claims 38, 39, 41, 44 – 48, 65, 69, and 71 – 80, 87, above, and in further view of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", 1971.

What is lacking from the teachings of Rennard, '362, and Remington is a teaching of triturations or solid solutions. These terms, as used and defined in the disclosure, are understood to have the same meaning as the term "solid dispersion" as used in the Chiou and Ghebre-Sellassie references.

The Chiou reference teaches the use of solid dispersions to increase the availability of poorly water soluble drug (1281 – 1283).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use a solid dispersion of the drug and PVP, as suggested by Chiou. The motivation is Chiou's teaching that this increases bioavailability of the drug. As discussed above, Ghebre-Sellassie also teaches that granulation methods may produce solid dispersions. The artisan would enjoy a reasonable expectation of success because Chiou and Ghebre-Sellasie teach how to make these types of compositions.

Claim 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 2003/0018071 to Rennard in view of US 6,677,362 to Ghebre-Sellassie and Remington: The Science and Practice of Pharmacy, 1995 (cited on PTO 892 mailed 11/3/2006), as

applied to claims 38, 39, 41, 44 – 48, 65, 69, and 71 – 80, 87, above, and in further view of Hatzelmann et al., of record (see IDS filed 6/1/2006).

What is lacking from the teachings of Rennard, '362, and Remington is a the N-oxide of the pyridine of the compound (corresponding to the N-oxide of roflumilast).

Hatzelmann teaches that roflumilast and its N-oxide are both useful as pharmaceutical agents and as PDE 4 inhibitors (abstract, materials and methods sections).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use the N-oxide of roflumilast in the pharmaceutical dosage form. Obviousness stems from both roflumilast and its N-oxide being recognized as pharmaceuticals useful for the same purpose. As such the artisan would enjoy a reasonable expectation of success.

(10) Response to Argument

1. The rejection of claims 68 and 82-84 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement.

Appellants first argue that the artisan would understand the meaning of "weight average molecular weight" and would understand it to be adequately disclosed. This argument is a straw-man. The issue is not whether the meaning of "weight average molecular weight" is known and disclosed; the issue is whether the original disclosure discloses that the average molecular weights of PVP listed therein are weight average molecular weights.

Appellants can only point to one portion of the original disclosure that allegedly supports the notion that the molecular weights referred to in are weight average molecular weights. Appellants rely on page 7 of the specification which discusses various Kollidon polymers. The different Kollidons have alpha numeric codes associated with them, such as Kollidon 12 PF, Kollidon 25, and Kollidon 90 F. Appellants continue that, the PVP manufacturer's information sheet gives the weight average molecular weight for PVP having various "K values," each K value being known in the art to correspond to a weight average molecular weight. Appellants conclude that from this the artisan would recognize that the molecular weights referred to in the specification are weight average molecular weights.

Appellants' argument is flawed. The molecular weights associated with the Kollidons in the specification do not match up with the weight average molecular weights for PVP having corresponding K values. For example, the specification, discloses that Kollidon 30 has a molecular weight of 44,000-54,000 daltons, whereas PVP with a K value of 30 has a weight average molecular weight of 66,800 daltons. Because the alpha numeric codes of Kollidon do not match to the K values, the fact that the artisan understands the meaning of K values (a term of art) does not have any bearing on the artisans understanding of the alpha numeric codes associated with Kollidons. Furthermore, Kollidon is a trademark. It is well established that a trademark specifies the source of goods, but not the nature of the goods. Because Kollidon,

whatever its alpha numeric code, does not specify the nature of a material[1], it cannot provide support for the concept that the molecular weights referred to throughout the specification are weight average molecular weight.

2. The rejection of claims 38, 39, 41, 45-48, 65, 69, 71-79, 81, and 87 under 35 U.S.C. 103(a) over Rennard in view of Ghebre-Sellassie and Remington.

Appellants first argue that specific limitations of the claims are not taught. In this vein, appellants first argue that Rennard does not teach the use of PVP. But the rejection at issue is not Rennard alone. In a rejection over more than one reference, arguments that do not consider all of the references cannot be persuasive. Both Ghebre-Selassie and Remington teach the use of PVP in granulation processes.

Appellants next argue that Ghebre-Sellassie does not disclose granulating with an aqueous solution of PVP. Appellants continue that this reference only teaches "solvent-free" granulation. Contrary to Appellants position, Ghebre-Sellassie teaches granulation on a fluid-bed apparatus. Fluid bed granulation is a wet granulation method, as described in further detail in Remington. That claim 1 in Ghebre-Sellassie may teach solvent-free methods does not negate that the reference also teaches fluid-bed granulation. Even if Ghebre-Sellassie only taught dry granulation (which is not the case) Remington discusses the various advantages of fluid-bed granulation over dry granulation.

Appellants also argue that Remmington does not disclose a process for producing a dosage form using an aqueous PVP solution. Contrary to this allegation,

[1] Appellants specification indicates that Kollidon is used to refer to PVP – well and good, an applicant for

Remington specifically notes (on page 1618) that, in granulation processes, PVP is a binder that is used in aqueous solvents. Remington also notes that in a fluid-bed process a solution or solvent is sprayed on the bed of suspended particles, and the rate of addition of binder (in the solution) is controlled. So Remington does suggest the use of a binder in solution in a fluid-bed granulation process, and suggests PVP specifically may be an aqueous solution.

Appellants further argue that there is no motivation to modify the references as proposed by the examiner. Essentially, Appellants argue that Ghebre-Sellassie method is a solvent free method of spraying on a PVP/drug mixture, whereas instant method requires granulation with a PVP solution. Appellants allege that the use of an aqueous PVP solution would not "absolutely and completely not result in Ghebre-Sellassie's intended composition." Appellants conclude that because no prior art teaches replacing the PVP that is mixed with the drug in Ghebre-Sellassie with aqueous PVP that is sprayed, as taught by Remington, there is no motivation to combine.

In response, Appellants seem to misunderstand or misconstrue the Examiners position. Ghebre-Selassie teaches mixing drug and PVP and then spraying further excipients, such as plasticizer and solubilizer, on this mixture in a fluid-bed granulation process. Remington teaches that, in fluid-bed granulation processes, it is customary to include binders in the spraying solution. One example of such a binder is PVP in an aqueous solution. Thus it would be merely following the customary practice in the art to include PVP as a binder in the spraying solution.

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a patent may be their own lexicographer. But there is no indication that the molecular weights are weight

Put another way, the difference between the Rennard/Ghebre-Sellassie and the claims is not, as Appellants aver, that the claims require removal of PVP from the core of Ghebre-Selassie and use of PVP as an aqueous solution in the granulating spray. Removal of PVP from Ghebre-Sellassie's core is not required by the claims, which provide that the drug is "mixed with one or more pharmaceutical excipients" before granulating. The difference between Rennard/Ghebre-Sellassie and the claims is only that the claims require that the granulating liquid in the fluid bed granulator include an aqueous solution of PVP, whereas Ghebre-Sellassie does specifically provide for the inclusion of PVP in the granulating solution. Remington, however, indicates that it is common practice to include binders in wet granulation fluid, that PVP is an appropriate binder, and that PVP is to be used in aqueous of alcoholic solutions. Given Ghebre-Selassie's preference of PVP as a binder, its selection would have been obvious.

Appellants then argue that there is some unexpected result in compositions prepared by the claimed method. Appellants point to page 11 of the specification, which alleges that the inventive methods produce dosage forms have increased bioavailability. In view of Ghebre-Sellaisse's teaching of increased bioavailability, this result is not surprising or unexpected. Furthermore, there is no evidence on record supporting the contention of unexpected results; Appellants merely make the allegation that the results are unexpected without any comparative data for support.

Appellants' comments about the Chiou reference are not well understood in view of this rejection. Chiou is not relied upon in this rejection,but is relied upon in other

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averages, nor does the trademark "Kollidon" convey this concept.

rejections for teaching the advantages of solid-dispersions. Appellants point to sections of Chiou alleging that PVP/drug solid dispersions can only be prepared by solvent methods (meaning not by granulation). This teaching is not relevant to this rejection, because the claims at issue here do not require solid dispersions. Nonetheless, Ghebre-Sellassie teaches producing solid dispersions of drug and PVP by a granulation method, disclosing in the Abstract that the compositions are solid dispersions. It is not surprising that in the twenty-three years between the publication of Chiou (1971) and filing date of Ghebre-Sellassie (1994), new methods of making solid dispersions, previously thought impossible, have been developed. Indeed, Ghebre-Sellassie, which does not mention a solvent method of forming solid dispersions, is entitled "Solid Drug Pharmaceutical Dispersions."

Appellants' last argument is deals with expectation of success. Their argument is that there would be no likelyhood to succeed in modifying the Chiou method by the other pieces of prior art. Appellants constantly point to Chiou here, but the Examiner cannot understand why. This rejection does not include the Chiou reference, and so the Examiner has not suggested that the Chiou reference be modified to meet the limitations of these claims. Nonetheless, as discussed above, Chiou's teachings about methods of making solid dispersions must be looked in view of all of the prior art, including Ghebre-Sellassie. The artisan is not an automaton. When Chiou, in 1971, stated that PVP/drug solid dispersions could only be made by a solvent method, but Ghebre-Sellassie in 1994 made PVP/drug solid dispersions by another method, the artisan would understand that Chiou is merely out of date on that point.

3. The rejection of claims 68 and 82 – 84 under 35 U.S.C. 103(a) over Rennard in view of Ghebre-Sellassie. Remington, and Login

Although Appellants make a separate section to address this rejection, the only argument is that Login fails to remedy alleged deficiencies in the other references. For the reasons discussed above, there are no deficiencies in the other references.

4. The rejection of claims 42-44, 53, 54, 85, and 86 under 35 U.S.C. 103(a) over Rennard in view of Ghebre-Sellassie. Remington, and Chiou.

Appellants 'arguments here are directed to Chiou. Because the claims at issue require solid dispersions, these arguments are germane to this rejection. Appellants argue that because Chiou teaches that PVP/drug dispersions can only be formed by the solvent method, and Ghebre-Sellassie mixes drug and PVP without solvent (before granulation), the artisan would not be able to make solid dispersions as claimed. Instead, according to Appellant, an artisan desiring solid dispersions would avoid the methods of Ghebre-Sellassie.

In making this argument, Appellants completely ignore that Ghebre-Sellassie teaches solid dispersions of PVP and drug, and does not use the "solvent method" of Chiou to make them. The artisan would not be troubled by this apparent contradiction. Chiou was published in 1971, Ghebre-Sellassie filed for his patent in 1994. In the twenty-three intervening years, Ghebre-Sellassie recognized that it is possible to do what Chiou thought could not be done: making a PVP/drug dispersion by a method other than the solvent method. The artisan would understand that Chiou is merely somewhat out of date on this point. At the time that the instant application was filed, the

artisan would know how to make a PVP/drug dispersion by the means disclosed in Ghebre-Selassie, and would be undeterred by the fact that in 1994 it was possible to do that which, in 1971, was deemed impossible. This is not a case where the prior art indicates that it would not be possible to do what Appellants' have done – this is a case where the prior art teaches how to do exactly what Appellants have done.

Even if, only for the sake of argument, the artisan believed that solid dispersions of drug and PVP could only be formed by dissolving PVP and drug in a solvent and then evaporating the solvent (as per Chiou), the claims would still be obvious. Ghebre-Sellassie mixes drug and PVP by blending the two before granulation. Col. 4, line 9 *et seq.* Chiou, in forming a solid dispersion, also mixes the drug and PVP. Thus, the artisan, recognizing the benefits of both Chiou's solid dispersion and of granulation according to Ghebre-Selassie and Remington, would seek to obtain both benefits. This would be simple to do - instead of combining the drug and PVP by blending (as in Ghebre-Selassie), the artisan would combine them by making a solid dispersion (as in Chiou). The artisan would then continue the granulation process as taught by Ghebre-Sellassie and Remington, using the solid dispersion instead of the blend. This would result in the claimed invention, and the artisan would expect to get the dual benefits of solid Chiou's solid dispersion and Ghebre-Selassie/Remington's granulation. Even if granulation alone could not form a solid solution, the rejection is still proper because granulation could be preformed after the solid dispersion is made.

5. The rejection of claims 68, 70, and 82-84 under 35 U.S.C. 103(a) over Rennard in view of Ghebre-Sellassie. Remington, and Hatzelmann.

Although Appellants make a separate section to address this rejection, the only argument is that Hatzelmann fails to remedy alleged deficiencies in the other references. For the reasons discussed above, there are no deficiencies in the other references.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, the rejections should be sustained.

Respectfully submitted,

/Eric E Silverman/

Examiner, Art Unit 1618

Conferees:

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617